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Comparative Effectiveness of Risperidone Long-Acting Injectable vs First-Generation Antipsychotic Long-Acting Injectables in Schizophrenia: Results From a Nationwide, Retrospective Inception Cohort Study

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Objective: **To compare in a generalizable sample/setting objective outcomes in patients receiving first-generation antipsychotic long-acting injectables (FGA-LAIs) or risperidone-LAI (RIS-LAI).** ***Methods:*** **Nationwide, retrospective inception cohort study of adults with International Classification of Diseases-10 schizophrenia using Danish registers from 1995 to 2009 comparing outcomes between clinician's/patient's choice treatment with FGA-LAIs or RIS-LAI. Primary outcome was time to psychiatric hospitalization using Cox-regression adjusting for relevant covariates. Secondary outcomes included time to all-cause discontinuation and psychiatric hospitalization in patients without LAI possession gap >28 days, and number of bed-days after psychiatric hospitalization.** ***Results:*** **Among 4532 patients followed for 2700 patient-years, 2078 received RIS-LAI and 2454 received FGA-LAIs (zuclopenthixol decanoate = 52.2%, perphenazine decanoate = 37.2%, haloperidol decanoate = 5.0%, flupenthixol decanoate = 4.4%, fluphenazine decanoate = 1.3%). RIS-LAI was similar to FGA-LAIs regarding time to hospitalization (RIS-LAI = 246.2 ± 323.7 days vs FGA-LAIs = 276.6 ± 383.3 days; HR = 0.95, 95% confidence interval (CI) = 0.87–1.03, *P* = 0.199) and time to all-cause discontinuation (RIS-LAI = 245.8 ± 324.0 days vs FGA-LAIs = 287.0 ± 390.9 days; HR = 0.93, 95% CI = 0.86–1.02, *P* = 0.116). Similarly, in patients without LAI discontinuation, RIS-LAI and FGA-LAIs did not differ regarding time to hospitalization (RIS-LAI = 175.0 ± 268.1 days vs FGA-LAIs = 210.7 ± 325.3 days; HR = 0.95, 95% CI = 0.86–1.04, *P* = 0.254). Finally, duration of hospitalization was also similar (incidence rate ratio = 0.97, 95% CI = 0.78–1.19, *P* = 0.744). Results were unchanged when analyzing only patients treated after introduction of RIS-LAI.** ***Conclusions:*** **In this nationwide cohort study, RIS-LAI was not superior to FGA-LAIs regarding time to psychiatric hospitalization, all-cause discontinuation, and duration of hospitalization. Given the cost of hospitalization and second-generation antipsychotic (SGA)-LAIs, these findings require consideration when making treatment choices, but also need to be balanced with the individual relevance of adverse effects/patient centered outcomes. In future, head-to-head trials and additional nationwide database studies including other SGA-LAIs is needed.**

Key words: schizophrenia/long-acting injectable/risperidone/first-generation antipsychotics/hospitalization/all-cause discontinuation/cohort study

Introduction

Despite treatment advances,[1] schizophrenia remains one of the most disabling disorders.[2] In addition to partial response and treatment refractoriness, relapses contribute to the morbidity and mortality associated with schizophrenia.[3,4] One established risk factor for inadequate treatment response and relapse is antipsychotic nonadherence.[5] Nonadherence is frequent in all areas of medicine.[6] However, for many reasons, including lack of insight, cognitive dysfunction, stigma, etc, patients with schizophrenia are at particular high-risk for nonadherence.[7] Measuring and identifying nonadherence is a challenge; underreporting is frequent and clinicians are generally poor in judging their patients' adherence.[5,7]

While external reminders and psychosocial interventions may improve nonadherence in schizophrenia,[5,8] long-acting injectable antipsychotics (LAIs) have been developed to address nonadherence through biweekly/monthly injections. Although patients have to return

for injections, clinicians and family members are certain when a medication dose has been received or missed, allowing immediate action. Moreover, since LAIs release the medication slowly, missing an injection will not lead to a precipitous drop in the blood level like after stopping oral antipsychotics (OAPs), increasing the window of protection during which nonadherence can be addressed.

LAIs are considered an important treatment option for nonadherent patients.[9] In a recent meta-analysis of 65 randomized controlled trials (RCTs) lasting ≥6 months (n = 6493), both OAPs and LAIs were significantly superior to placebo in preventing relapses in schizophrenia.[4] Moreover, in an indirect comparison, LAIs (studies = 7) prevented relapse significantly more than OAPs (studies = 14). However, results from studies directly comparing LAIs with OAPs are more complicated. For example, a recent meta-analysis of 5176 patients (studies = 21) found no difference between LAIs and OAPs.[10] Nevertheless, the lack of superiority of LAIs was possibly due to factors inherent in RCTs that challenge the generalizability of these findings, including recruitment of patients who are likely more adherent and less severely ill than those receiving LAIs in clinical practice, and whose adherence may be measured and is enhanced by frequent study visits or provision of OAPs.[10] Supportive of this argument are results of a meta-analysis of 25 mirror image studies (n = 5940), in which 23 of the 25 studies individually showed LAI superiority for reducing hospitalizations in the same individuals switching from an OAP to LAI.[11] However, one needs to consider that in mirror image studies in general, a time or order effect can affect outcomes and that in prospective mirror image studies participation in study procedures could bias results in favor of the second, LAI period. Support also comes from another meta-analysis in which pooling of results from 5 RCTs did not show a difference between LAIs and OAPs regarding hospitalization, while in four mirror image studies and four cohort studies each LAIs were superior to OAPs.[12] Notably, nationwide cohort studies,[13] included in the latter meta-analysis, have the strong advantage of giving a representative picture of LAI effects under real-world conditions. Although a nationwide naturalistic database includes treatment approaches that are and that are not guideline or evidence based, the interventions are used under conditions that reflect existing constraints, and the data base includes the entire cohort of treated patients, thereby providing a test of performance of the studied treatments in the environment in which they will have to perform.

Although relapse and hospitalization are more cost-intensive than medications,[14] second-generation antipsychotic (SGA)-LAIs are more expensive than first-generation antipsychotic (FGA)-LAI alternatives. Although the oversimplified dichotomy between FGAs and SGAs has likely outlived its utility,[15] a finding from the most recent meta-analysis of RCTs of OAPs vs LAIs is of interest.[10] Whereas pooled analyses did not show superiority of LAIs, analyzing FGA-LAIs and SGA-LAIs separately, FGA-LAIs were significantly superior to OAPs in preventing relapse (studies = 10, P = .02). Conversely, SGA-LAIs did not separate from OAPs (studies = 11, P = 1.0). Individually, too, neither olanzapine-LAI nor risperidone-LAI (RIS-LAI) were superior to OAPs regarding relapse/other relapse-related outcomes. Nevertheless, the superiority of FGA-LAIs was moderated by publication year. In trials published until 1991, consisting exclusively of fluphenazine-LAI studies, LAIs were superior to OAPs (P = .02), while this was not the case in the newer RCTs published since 2005 (P = .94), which included only 2/10 FGA-LAI studies.[10] However, these findings were based on an indirect comparison across several decades. Thus, findings could be due to time trends in the treatment and service delivery, including differences in patient illness severity, OAP comparator doses, thresholds for declaring relapse, etc, each potentially favoring LAIs in older trials. Therefore, direct comparisons of FGA-LAIs with SGA-LAIs are needed.[10]

In contrast to the LAI data reviewed above, two recent meta-analyses comparing oral SGAs with oral FGAs for relapse prevention and hospitalization in chronic[3] and first-episode[16] schizophrenia patients, each found significant advantages for SGAs, albeit with modest effect sizes, translating into a number-needed-to-treat of 17.[3] Since this difference could be due to worse adherence with oral FGAs due to greater extrapyramidal side effects, it is unclear if relapse prevention advantages of SGAs would extend to LAI formulations.

The comparative effectiveness of expensive SGA-LAIs vs cheaper FGA-LAIs is an important and largely unexamined question. Given health care cost pressures and the high personal and societal burden of relapses in schizophrenia and to overcome the bias inherent in RCTs examining this issue, we conducted a nationwide cohort study to assess the relative effects on relapse/hospitalization of FGA-LAIs vs RIS-LAI, a widely used SGA-LAI. Based on the meta-analytic data on hospitalization risk with oral antipsychotics,[3,16] we hypothesized that RIS-LAI would be superior to FGA-LAIs regarding hospitalization and all-cause discontinuation.

Methods

Design

This was a retrospective inception cohort study using data from the nation-wide Danish registers. In Denmark, all diagnoses assigned throughout the country are reported to the Danish Central Psychiatric Research Register (DPCRR), which contains complete electronic data from 1969 onwards.[17] The diagnostic validity of the schizophrenia diagnosis in the DPCRR has proven to be high, and the register has contributed significantly to epidemiological research.[18,19]

Ethical and data use approval for the study was approved by the Danish Data Protection Agency, National Board of Health and Statistics Denmark.

Sample

Subjects for the analyses had a lifetime diagnosis of International Classification of Diseases (ICD-10 F20) schizophrenia in the DPCRR[17] from January 1, 1995 to December 31, 2009. All patients with schizophrenia filling ≥1 outpatient LAI prescription in Denmark during the study period were included, as there is only one psychiatric health care system and all prescriptions are recorded in the national prescription database.

Treatment

Prescription data for included subjects were obtained from the national prescription database, containing information about the number of sold defined daily dosages (DDD) of all outpatient prescription-based medications. DDDs are assigned and reviewed by researchers of the World Health Organization Collaborating Centre of Drug Statistics Methodology. Medication status during inpatient treatment was not available. Only incident periods of FGA-LAIs or RIS-LAI were included in the analysis and all patients were followed for up to 5 years. Continued treatment was defined as renewing prescription for the same LAI based on pack size, assuming that LAI injection intervals were 14 days and that each patient used one vial per injection. Saving remaining vials for a next injection or sharing prescription-based medicine between patients is not allowed in Denmark.

From 1995 to 2009, the following FGA-LAIs were available in Denmark: zuclopentixol-decanoate, haloperidol-decanoate, perphenazine-decanoate, fluphenazine-decanoate, and flupenthixol-decanoate. RIS-LAI became available in Denmark in 2003. Only patients agreeing with LAIs were included, since no compulsory LAI treatment was allowed in Denmark.

Outcomes

Primary outcome was time to psychiatric hospitalization; secondary outcome was time to all-cause discontinuation. Additionally, we compared RIS-LAI with FGA-LAIs regarding time to hospitalization in patients without LAI possession gap >28 days and number of bed-days after treatment failure for psychiatric hospitalization.

Time to Hospitalization

In the time to psychiatric hospitalization model, patients were censored at death, after 5 years follow-up, switch between LAI treatments or filling an OAP prescription after a ≥2-week gap of filling the LAI prescription, whichever came first. The latter censoring criterion was used to censor patients who were switched intentionally, by patient's or the prescriber's decision, to oral treatment. For the sensitivity analysis of patients with hospitalization before LAI discontinuation patients were censored when the LAI possession gap exceeded 28 days.

Time to All-Cause Discontinuation

Time to all-cause discontinuation was chosen as a combined outcome, reflecting both patient's/family's and prescriber's decisions for discontinuation, including inefficacy, intolerability, nonadherence, and non-medication related factors. An additional 14-day gap between injections was allowed before patients were considered as having discontinued the LAI. Patients switched from one FGA-LAI to another FGA-LAI were considered as having discontinued treatment.

Covariates

The following covariates were used to adjust for confounding by indication or severity of schizophrenia: illness duration, sex, time of LAI initiation, percentage of time with psychiatric hospitalization during the last 2 years, receiving disability pension, prior clozapine use, number of psychiatric and non-psychiatric co-medications, and LAI initiation during inpatient vs outpatient status. Initiating LAIs during inpatient status was defined as patients picking up their first LAI prescription within 4 weeks after hospital discharge. Adjustment for dose variation among individuals was not possible because with FGA-LAIs the full vial content is not necessarily injected.

Since OAP treatment is common during LAI treatment and may affect the outcome, we adjusted for OAP cotreatment in regression models. However, the first 2 months were excluded from creating this covariate because it is recommended to use oral risperidone for ≥3 weeks after the first RIS-LAI injection due to delayed absorption. Furthermore, we specified whether a different or the same OAP compared to the LAI was used adjunctively, as the former may reflect lack of LAI monotherapy efficacy or attempt to reduce adverse effects, whereas as the latter more likely reflects the need for quick dose adjustment. We reported both rates of patients filling only one prescription from the pharmacy and rates of patients filling ≥2 prescriptions during the study period.

The number of non-antipsychotic psychiatric co-medications at baseline during the first 3 months was defined as picking up at least one prescription of the following drugs/drug groups: antidepressants (N06A+N06C), stimulants (N06B), anti-dementia drug (N06D), clonazepam (N03AE01), valproate (N03AG01), lamotrigine (N03AX09), carbamazepine (N03AF01), oxcarbazepine (N03AF02), lithium (N05AN), and psycholeptics (anxiolytics, sedatives, anxiolytics) (N05B+N05C).

The number of non-psychiatric medications was defined as any other drug not listed above.

Since RIS-LAI was not available before 2003, RIS-LAI patients entered the survival analysis later than FGA-LAI patients. Since hospitalization depends on multiple factors, we assessed secular trends in number of psychiatric hospitalizations, bed-days, and interval between hospitalizations (truncated at the maximum follow-up time of this study = 5 years) for all Danish schizophrenia

Table 1. Secular Trends in Psychiatric Admissions and Bed Days Based on 26 230 Schizophrenia Patients

	Admissions		Bed Days		Days Between Last Discharge and New Admission	
Year	Mean	95% CI	Mean	95% CI	Mean[a]	95% CI
1995	1.77	1.74–1.81	105.2	104.9–105.5	402.8	402.2–403.4
1996	1.87	1.84–1.91	103.1	102.8–103.3	390.3	389.7–390.9
1997	1.83	1.79–1.86	105.1	104.9–105.4	393.9	393.3–394.5
1998	1.88	1.85–1.91	102.2	101.9–102.4	408.3	407.7–408.9
1999	1.93	1.89–1.96	100.9	100.6–101.1	380.4	379.8–381.0
2000	1.87	1.84–1.91	97.0	96.7–97.2	411.7	411.1–412.3
2001	1.96	1.92–1.99	91.4	91.1–91.6	392.4	391.9–393.0
2002	1.97	1.93–2.00	91.0	90.8–91.2	414.3	413.8–414.9
2003	1.93	1.90–1.97	86.8	86.6–87.1	427.9	427.4–428.5
2004	1.94	1.91–1.98	84.9	84.7–85.1	431.0	430.4–431.5
2005	1.96	1.92–1.99	81.1	80.9–81.3	459.2	458.6–459.8
2006	2.01	1.97–2.04	79.4	79.2–79.6	452.8	452.2–453.4
2007	2.08	2.05–2.12	77.8	77.6–78.0	461.8	461.2–462.4
2008	2.19	2.15–2.23	74.5	74.3–74.7	433.0	432.5–433.6
2009	2.27	2.23–2.31	70.8	70.6–71.0	443.9	443.3–444.4
Slope[b]	0.01	$P < .001$	−0.03	$P < .001$	0.01	$P < .001$

Note: [a]With values truncated at 5 years (1826 days).
[b]Estimated from negative binomial regression analyses using calendar year as explanatory variable.

patients (ICD-10 F20) during the years 1995–2009 ($n = 26\,230$). During the study period, both the number of admissions and time to hospitalization increased, while the number of bed-days decreased significantly (Table 1). Therefore, we added year of LAI initiation as a covariate in all regression analyses. In addition, we conducted a sensitivity analysis only including patients entering the analysis from 2003 onwards.

Statistical Analyses

Statistical analyses were performed with STATA 12 at Statistics Denmark server via remote access. Sample characteristics were compared between RIS-LAI and FGA-LAIs using Student's *t* test or Wilcoxon rank sum test, whichever appropriate, for continuous variables, and using chi-squared test for categorical variables. For all survival analyses, a Cox-regression survival analysis was conducted to obtain hazard ratios (HR) with 95% confidence intervals (CI) indicating risk modeled as time to the respective event. All models were tested for proportional hazards with estat phtest commands in STATA, which used the residuals of Schoenfeld, and were evaluated graphically. The covariates listed above were used as explanatory variables aiming to identify relevant moderators of the respective outcomes. Countable data, such as number of bed-days after treatment failure for psychiatric admission were compared between RIS-LAI and FGA-LAIs using negative binomial regression analysis and the same covariates as above because of the overdispersed distribution, which is common in observational studies reflecting sample heterogeneity.

Results

A total of 4532 patients initiating LAIs were identified; 2078 (45.9%) initiated RIS-LAI and 2454 (54.1%) initiated FGA-LAIs. Total follow-up time was 4700 patient-years. Sample characteristics are shown in Table 2. Compared with patients initiating FGA-LAIs, RIS-LAI patients were younger (35.8 ± 12.5 vs 39.0 ± 13.4 years, $P < .001$) and more male (59.6% vs 55.6%, $P = .006$). Additionally, RIS-LAI patients had characteristics associated with less illness severity than FGA-LAI users (eg, lower percentage of prior inpatient time, less patients receiving disability pension and living in an institution), except for longer duration of schizophrenia diagnosis ($P < .001$). Moreover, patients on RIS-LAI had more outpatient contacts per month (1.8 ± 2.4 vs 1.2 ± 1.9, $P < .001$).

Time to Psychiatric Hospitalization

RIS-LAI was not different from FGA-LAIs in adjusted Cox regression analyses regarding time to hospitalization in all patients (2710.9 patient-years: HR = 0.95, 95% CI = 0.87–1.03, $P = .199$) (Table 3, Figure 1) and in patients without prespecified LAI possession gap (1691.1 patient-years: HR = 0.95, 95% CI = 0.86–1.04, $P = .254$) (Table 3). In the sensitivity analysis of patients first initiating LAI treatment after 2003, RIS-LAI was also not superior to FGA-LAI (HR = 1.03, 95% CI = 0.93–1.13, $P = .572$) (Table 4).

Time to All-Cause Discontinuation

RIS-LAI was not significantly different from FGA-LAIs regarding time to all-cause discontinuation (2892.7 patient-years: HR = 0.94, 95% CI = 0.86–1.02, $P = .116$) (Table 3, Figure 1). Sensitivity analyses were consistent with the primary results (HR = 1.01, 95% CI = 0.92–1.11, $P = .839$) (Table 4).

Number of Bed-Days After Failure Due to Psychiatric Hospitalization

Number of bed-days was significantly higher in the FGA-LAI group, 233.4 (463.6) vs 159.6 (SD = 294.7). However, in the adjusted binomial regression analyses, RIS-LAI and FGA-LAIs did not differ regarding the duration of hospitalization (IRR = 0.97 95% CI = 0.78–1.19, $P = .744$) (Table 3). Sensitivity analyses were consistent with the primary results (IRR = 1.06, 95% CI = 0.84–1.32, $P = .632$) (Table 4).

Discussion

This is the largest study to investigate the real-world effects of RIS-LAI, the first and most used SGA-LAI,

Table 2. Sample Characteristics

	Total (N = 4532)		Risperidone-LAI (N = 2078)		Conventional-LAI (N = 2454)		
	Mean	SD	Mean	SD	Mean	SD	P Value
Age, years							
Onset of any psychiatric disorder	28.5	11.1	27.4	10.4	29.5	11.6	<.001
Onset of schizophrenia	35.0	13.2	32.7	12.3	37.0	13.7	<.001
Baseline (entering the survival analysis)	37.5	13.1	35.8	12.5	39.0	13.4	<.001
Male sex (N, %)	2603	57.4	1239	59.6	1364	55.6	.006
Started as inpatient (N, %)	298	6.6	125	6.0	173	7.1	.162
Year of initiation	2003.1	4.1	2005.9	1.9	2000.7	4.0	<.001
Percentage of time with psychiatric hospitalization (2 years prior of LAI initiation)	0.3	0.4	0.3	0.3	0.4	0.4	<.001
Duration of illness (years)							
From onset of schizophrenia diagnosis	2.5	2.9	3.1	3.2	2.0	2.6	<.001
From onset of first psychiatric diagnosis	9.0	8.2	8.4	7.8	9.6	8.5	<.001
Receiving disability pension (N, %)	2943	64.9	1225	59.0	1718	70.0	<.001
Exposure to clozapine (N, %)	374	7.1	181	8.7	193	7.9	.303
Mean number of outpatient contacts per month	1.5	2.2	1.8	2.4	1.2	1.9	<.001
Married (N, %)	321	7.1	93	4.5	228	9.3	<.001
Living situation (N, %)							
Alone	2897	63.9	1078	51.9	1819	74.1	<.001
In institution	459	10.1	142	6.8	317	12.9	<.001
Concomitant medications (N, %)							
Non-psychiatric medications	1.5	2.2	1.2	2.0	1.8	2.3	<.001
Psychiatric co-medications	0.9	1.1	0.9	1.1	0.9	1.1	.550
Any oral antipsychotic after 2 months (N, %)[a]	1342	44.3	626	45.2	716	43.6	.377
Same oral antipsychotic as intervention	554	18.3	298	21.5	256	15.6	<.001
Other oral antipsychotic than intervention	1032	34.1	454	32.8	578	35.2	.165
Any oral antipsychotic (min. 2 pick-ups) after 2 months (N, %)[a]	1100	36.3	513	37.0	587	35.7	.459
Same oral antipsychotic as intervention (min. 2 pick-ups)	385	12.7	208	15.0	177	10.8	.001
Other oral antipsychotic than intervention (min. 2 pick-ups)	855	28.2	367	26.5	488	29.7	.051
Antipsychotic DDD's (oral and LAI) last year before baseline[b]							
Total	0.98	1.10	0.95	1.15	1.01	1.06	<.001
Adjusted for number of bed-days	1.57	1.98	1.29	1.60	1.83	2.24	<.001
Type of first-generation antipsychotic long-acting injectable (N, %)							
Fluphenazine decanoate			—	—	31	1.3	—
Perphenazine decanoate			—	—	912	37.2	—
Haloperidol decanoate			—	—	123	5.0	—
Flupentixol decanoate			—	—	107	4.4	—
Zuclopenthixol decanoate			—	—	1281	52.2	—

Note: FGA-LAI, first-generation antipsychotic long-acting injectable.
[a]In total, 3027 patients "survived" the first 2 months. The risperidone group includes 1385 patients, and the conventional group includes1642 patients. Percentages are calculated based on these groups.
[b]152 patients from the conventional group were excluded because 1-year follow-up before baseline was not possible. Calculation is based on N = 2302.

compared to FGA-LAIs regarding the important outcomes of relapse/hospitalization and duration of hospitalization in schizophrenia. Our major finding is that, contrary to our hypotheses, RIS-LAI was not superior to FGA-LAIs regarding time to hospitalization, adjusting for relevant covariates and taking into account whether or not patients stopped filling LAI prescriptions, regarding time to all-cause discontinuation and duration of hospitalization after treatment failure. Additionally, as described before,[20,21] many patients discontinued treatment and/or relapsed early after initiating LAIs. In a previous data base study of schizophrenia patients, the mean duration of LAI treatment episodes was only 71.7 ± 56.4 days for haloperidol-LAI, 58.3 ± 53.6 days for fluphenazine-LAI, and 60.6 ± 48.8 days for RIS-LAI.[21]

Since number of hospitalizations increased during the latter part of the study and since patients on RIS-LAI had longer illness duration, the lack of superiority of RIS-LAI compared to FGA-LAIs could be due to a greater likelihood of admissions in the later years or due to greater illness chronicity. However, we adjusted the Cox-regression analyses for year of initiating LAI and illness duration, and RIS-LAI patients also had characteristics pointing toward lower illness severity and risk

Table 3. Cox Regression and Negative Binomial Regression Analysis Results

	Time to Hospitalization (All Patients)			Time to All-Cause Discontinuation			Time to Hospitalization (Patients Without LAI possession Gap >28 Days)			Number of Bed-Days After Failure for Hospitalization		
	N = 4532 (3765 Failures)			*N* = 4532 (3933 Failures)			*N* = 4532 (3157 Failures)			*N* = 3765		
	2710.9 patient-years			2892.7 patient-years			1691.1 patient-years			N/A		
	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	IRR[b]	95%CI	*P* Value
Risperidone	0.95	0.87–1.03	.199	0.94	0.86–1.02	.116	1.03	0.93–1.15	.519	0.97	0.78–1.19	.744
Male sex	1.04	0.97–1.11	.274	1.04	0.98–1.12	.208	0.95	0.87–1.05	.302	1.12	0.96–1.30	.163
Year of depot initiation	1.01	1.00–1.02	.126	1.01	1.00–1.02	.055	1.08	1.05–1.11	<.001	0.93	0.91–0.96	<.001
Percentage of time with psychiatric hospitalization during 2 years prior to LAI intiation	1.93	1.75–2.13	<.001	1.88	1.71–2.06	<.001	2.19	1.88–2.55	<.001	7.23	5.81–9.00	<.001
Duration of illness	1.97	1.88–2.06	<.001	1.92	1.84–2.01	<.001	2.17	2.00–2.35	<.001	1.15	1.11–1.19	<.001
Disability pension	1.00	0.93–1.07	.903	1.00	0.94–1.08	.908	1.08	0.97–1.19	.159	1.18	1.00–1.39	.044
Clozapine	1.23	1.09–1.38	.001	1.20	1.07–1.35	.002	1.29	1.10–1.51	.002	2.46	1.90–3.19	<.001
Number of non-psychiatric medications	0.94	0.92–0.95	<.001	0.95	0.93–0.96	<.001	0.93	0.91–0.95	<.001	0.92	0.90–0.94	<.001
Number of psychiatric co-medications	1.07	1.03–1.10	<.001	1.06	1.03–1.10	<.001	1.07	1.03–1.12	<.001	0.83	0.77–0.89	<.001
Inpatient status at time of LAI initiation	0.75	0.64–0.88	<.001	0.77	0.66–0.90	.001	0.75	0.62–0.90	.002	0.85	0.63–1.16	.319

Note: IRR, incidence rate ratio.
[a]Cox regression analysis.
[b]Negative binomial regression analysis, IRR.

for hospitalization, including lower percentage of prior inpatient time, less patients receiving disability pension and living in an institution, factors we also adjusted for. Moreover, even when restricting the analyses to patients initiating LAI treatment from 2003 onwards when RIS-LAI was available yielded similar results as the main analyses.

Although the similar hospitalization risk of RIS-LAI and FGA-LAIs is consistent with results of broadly similar efficacy of oral antipsychotics for schizophrenia,[15,22,23] our results are in contrast to two recent meta-analyses that did show significant advantages of oral SGAs vs oral FGAs for relapse prevention/hospitalization.[3,16] However, these meta-analyses were also based on RCTs that include only a subset of patients treated nationwide, and samples were obviously much smaller than in this register study. Moreover, although multiple open label studies had shown advantages of a switch from OAPs or FGA-LAIs to RIS-LAI,[24–27] superiority of RIS-LAI over OAPs was not confirmed in the previously mentioned meta-analysis.[10] Similarly, superiority of switch to RIS-LAI over remaining on FGA-LAIs was also not confirmed in an RCT randomizing 66 adults with schizophrenia or schizoaffective disorder taking haloperidol-LAI (n = 40) or fluphenazine-LAI (n = 22) to stay on these LAIs or switch to RIS-LAI.[28] In analyses of the first 6 months conducted under protocol conditions, time to all-cause discontinuation was similar between the switch and stay groups. Conversely, including the subsequent 6-month naturalistic phase, patients switched to RIS-LAI stopped treatment earlier than those staying on FGA-LAIs (31% vs 10%, P = .01). LAI groups also did not differ regarding psychopathology, hospitalizations, sexual side effects, and new-onset tardive dyskinesia or extrapyramidal symptoms, while those switched to RIS-LAI had significantly greater increases in body mass index and prolactin.[28] Moreover, our findings are consistent with similar rehospitalization rates associated with RIS-LAI (29.4%) and FGA-LAIs (28.2%) in a small subsample of patients with first episode schizophrenia discharged on an LAI (RIS-LAI: N = 51; FGA-LAIs: N = 77) in a nationwide Finnish sample.[13] Although the hospitalization rates were lower than in our study, this is likely due to the fact that discontinuation was more frequent (RIS-LAI = 78.4%, FGA-LAIs = 98.7%). Additionally, our results in patients treated under naturalistic conditions are also consistent with the first, recently published, head-to-head, randomized controlled trial that compared paliperidone-LAI with haloperidol-LAI.[29] This study found that during follow-up of up to 24 months, both treatments had similar efficacy failure, defined as a psychiatric hospitalization, need for crisis stabilization, and substantial increase in frequency of outpatient visits, clinician's decision that oral antipsychotics could not be discontinued within 8 weeks after LAI initiation, or clinician's decision to discontinue the assigned LAI due to inefficacy. Nevertheless, both treatments differed significantly regarding some adverse effects.[29]

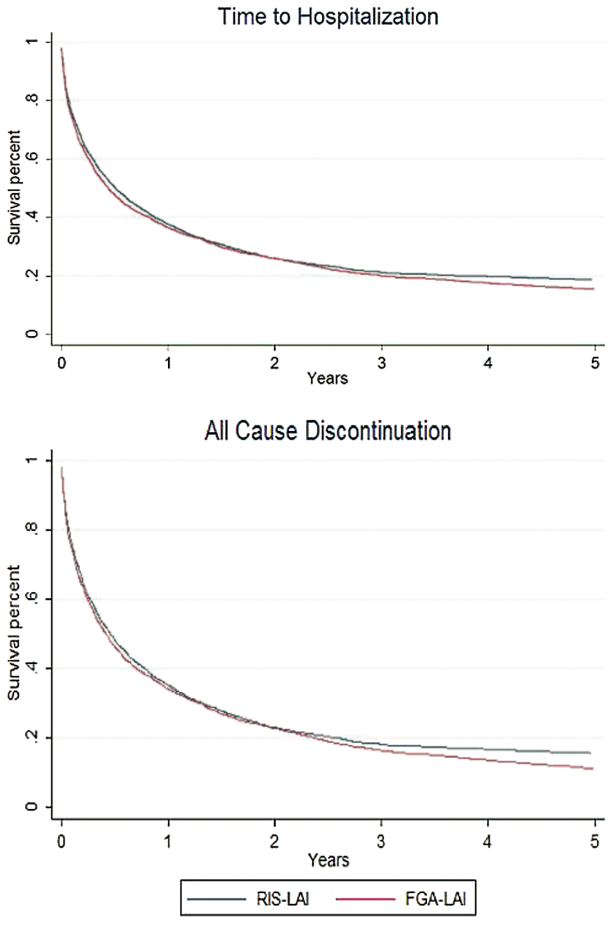

Fig. 1. Survival analysis curve of time to psychiatric hospitalization and time to all-cause discontinuation.

The mean age of onset of schizophrenia was rather high compared to other studies, which is explained by the fact that most of these patients were diagnosed in the past when less focus existed on early diagnosis and intervention. The age of onset of schizophrenia has been reduced substantially during the last decade in Denmark.[30] Moreover, we did not employ an upper age limit for first episode schizophrenia as used in most other first episode studies.

More than half of the patients in the FGA-LAI group were treated with zuclopenthixol-decanoate, which is not marketed in the US, but widely used in Scandinavia and UK. Since zuclopenthixol is an FGA,[31] the observed similar outcomes with FGA-LAIs was unlikely driven by unique efficacy of zuclopenthixol-LAI. Actually, one open study of 435 patients even suggested superiority of RIS-LAI regarding treatment persistence vs zuclopenthixol-LAI (P = .002) and all other FGA-LAIs (P = .009),[32] yet the samples were small and relevant covariates were not controlled for.

Expectedly, significant moderators of shorter time to hospitalization and higher all-cause discontinuation in the Cox-regression models included proxy measures of illness severity, including illness duration, percentage of time hospitalized in the preceding 2 years, higher number of psychotropics, and previous clozapine treatment. Conversely, variables associated with more supervision/health contact, such as initiating LAIs as an inpatient and higher number of non-psychiatric medications, were associated with a reduced likelihood of hospitalization and all-cause discontinuation.

Strengths of this study are its large sample and generalizability, including all schizophrenia patients initiating LAIs nationwide, many of which would be too sick or unwilling to participate in research, illustrated by the fact that >40% were hospitalized and 60% discontinued LAI within 6 months.

Despite its strengths, this study also has limitations. First, treatment allocation was not random. Therefore, risks of biases exist, such as difference in illness severity and effects of secular trends. Although there might be additional biases, we adjusted for many, if not most, relevant biases. Second, psychopathology, functional/quality of life and side-effect ratings, including tardive dyskinesia, were not available. Therefore, we cannot rule out that either RIS-LAI or FGA-LAIs may have advantages within some of these domains. Third, we assumed that each vial was equivalent to 14 days treatment, the main recommendation for all LAIs used in this study. Although, FGA-LAIs are traditionally administered biweekly in Denmark, some FGA-LAIs may have been administered every 3 or 4 weeks, which could have led to erroneous pronouncement of early termination, favoring RIS-LAI. Fourth, time of discontinuation was based on when LAIs were not filled from the pharmacy anymore. However, some patients may have stopped the LAI before using all vials, leading to overestimating the time until discontinuation. This might explain why the proportion of patients without a >28 day LAI possession gap at time of admission was rather high. Fifth, discontinuation rates in this study were higher than in some prior studies. This difference may be partly due to the fact that this study was a nationwide study including even the most severe patients. In addition, we focused in this inception cohort study on the incident LAI period. This approach may also have contributed to the results, as we included patients earlier in their illness course than most studies (mean age = 28 years) when nonadherence may be somewhat higher. Sixth, RIS-LAI was introduced during the second half of the study. This may have influenced findings through secular trend effects. Over the years, inpatient treatment shifted to outpatient services, as documented previously,[30] illustrated also by the lower number of bed-days and longer time between admissions. This shift to ambulatory care may have favored RIS-LAI in the time to psychiatric hospitalization model because of a higher threshold for admission. However, we adjusted Cox-regression analyses for time of study entry and results remained unchanged when restricting the analyses to patients treated after

Table 4. Sensitivity Analysis of Subjects Only Entering From 2003 or Later: Cox Regression and Negative Binomial Regression Analysis Results

	Time to Hospitalization (All Patients)			Time to All-Cause Discontinuation			Time to Hospitalization (Patients Without LAI possession Gap >28 Days)			Number of Bed-Days After Failure for Hospitalization		
	N = 2854 (2290 Failures)			*N* = 2854 (2404 Failures)			*N* = 2854 (1890 Failures)			*N* = 2290		
	1563.9 patient-years			1660.7 patient-years			966.3 patient-years			N/A		
	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	IRR[b]	95% CI	*P* Value
Risperidone	1.03	0.93–1.13	.572	1.01	0.92–1.11	.839	0.95	0.86–1.04	.254	1.06	0.84–1.32	.632
Male sex	0.97	0.89–1.06	.474	0.98	0.90–1.06	.586	1.04	0.96–1.12	.323	1.10	0.91–1.34	.334
Year of depot initiation	1.08	1.05–1.11	<.001	1.07	1.05–1.10	<.001	1.01	1.00–1.02	.256	0.92	0.88–0.97	.002
Percentage of time with psychiatric hospitalization during 2 years prior to LAI initiation	2.03	1.77–2.32	<.001	1.95	1.71–2.22	<.001	2.05	1.84–2.28	<.001	9.24	6.92–12.32	<.001
Duration of illness	1.89	1.78–2.01	<.001	1.87	1.76–1.98	<.001	2.28	2.15–2.42	<.001	1.15	1.11–1.19	<.001
Disability pension	1.03	0.94–1.14	.476	1.03	0.94–1.13	.473	1.03	0.95–1.11	.497	1.13	0.92–1.40	.235
Clozapine	1.23	1.06–1.42	.005	1.19	1.03–1.38	.016	1.27	1.12–1.44	<.001	3.20	2.35–4.36	<.001
Number of non-psychiatric medications	0.93	0.91–0.96	<.001	0.95	0.93–0.97	<.001	0.93	0.91–0.95	<.001	0.82	0.78–0.85	<.001
Number of psychiatric co-medications	1.08	1.04–1.12	<.001	1.07	1.03–1.12	<.001	1.07	1.03–1.12	.002	0.80	0.73–0.89	<.001
Inpatient status at time of LAI initiation	0.72	0.58–0.90	.004	0.76	0.61–0.94	.010	0.73	0.56–0.94	.014	0.77	0.51–1.16	.207

Note: IRR, incidence rate ratio.
[a]Cox regression analysis.
[b]Negative binomial regression analysis, IRR.

introduction of RIS-LAI into the Danish market. Additionally, RIS-LAI patients received more outpatient contacts during their follow-up because of the secular trend toward more treatment during outpatient status.[30] This may have favored patients entering the study in the last half of the study period. Seventh, we did not have access to reasons for discontinuation, which could have highlighted potential differences in efficacy or tolerability or which could have included switch to the new RIS-LAI in stable patients, as RIS-LAI had been touted as being superior and/or better tolerated than FGA-LAIs.[24–26] The latter motivation, would have favored RIS-LAI regarding all-cause discontinuation. Finally, the database contained RIS-LAI as the sole SGA-LAI. However, since RIS-LAI was either non-inferior to paliperidone-LAI[33] or outperformed paliperidone-LAI using a prespecified 5.5 point non-inferiority margin,[34] results may generalize to other SGA-LAIs, at least those with similar pharmacology, bearing in mind that among SGAs risperidone is closest to FGAs in its receptor binding profile and side effect propensity. The same applies to paliperidone LAI, which has recently been studied finding no differences compared to haloperidol-LAI.[29]

Although this study was not designed as a cost-effectiveness study, the study results should also be interpreted in the light of the cost of medication and psychiatric hospitalization. During the study period, the annual cost for RIS-LAI was approximately 7500 USD compared to 300 USD for FGA-LAIs. The costs for a psychiatric hospitalization was approximately 700 USD per day. The raw figures suggest that in Denmark FGA-LAIs would be more cost effective until up to 10 bed-days per year more than RIS-LAI patients. Obviously, this ratio will be different in different countries and settings, as it depends on the medication and inpatient cost that vary considerably. Moreover, the value of a cost-derived number of an additional 10 days per year that FGA-LAI treated patients could spend in the hospital without their care being more expensive than that of RIS-LAI treated patients needs to be evaluated vis-à-vis personal suffering during hospitalization and detrimental effects of relapse. Studies specifically investigating the cost effectiveness of SGA-LAIs vs FGA LAIs based on large naturalistic studies are warranted.

In conclusion, despite a 30-day longer time until hospitalization and 40-day longer time until all-cause discontinuation with RIS-LAI than FGA-LAIs over the entire treatment period, results were not statistically different between the two treatment groups, and this difference is of questionable clinical relevance. Moreover, although hospitalization days were 74 days shorter for RIS-LAI, this difference was also clearly not different (IRR = 0.97, *P* =

.744) when potentially confounding variables were entered into the analyses. This lack of difference in clinically relevant outcomes found in over 4500 patients, coupled with the higher cost for RIS-LAI and other SGA-LAIs, requires consideration when making treatment decisions. However, these findings should also be considered with the limitations of our study in mind, including its nonrandomized nature, lack of information on reasons for discontinuation, adverse effects, quality of life, subjective well-being, caregiver assessment of patients' status, the observed group differences in baseline and outpatient contact characteristics, the potential influence of secular trends over time with RIS-LAI being only available starting in 2003, and inclusion of FGA-LAIs not available in all parts of the world as well as inclusion of RIS-LAI as the sole SGA-LAI. Therefore, additional, large, simple, randomized trials are needed that evaluate the efficacy, tolerability and effectiveness of specific LAIs in the treatment of generalizable patient cohorts with schizophrenia who are managed in usual care environments.

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References

1. Kane JM, Correll CU. Past and present progress in the pharmacologic treatment of schizophrenia. *J Clin Psychiat*. 2010;71:1115–1124.
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163–2196.
3. Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CU. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. *Mol Psychiat*. 2013;18:53–66.
4. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379:2063–2071.
5. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiat*. 2009;70(suppl 4):1–46; quiz 47–48.
6. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv*. 1998;49:196–201.
7. Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry*. 2013;12:216–226.
8. Velligan D, Mintz J, Maples N, et al. A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. *Schizophrenia Bull*. 2013;39:999–1007.
9. Velligan DI, Weiden PJ, Sajatovic M, et al. Strategies for addressing adherence problems in patients with serious and persistent mental illness: recommendations from the expert consensus guidelines. *J Psychiatr Pract*. 2010;16:306–324.
10. Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40:192–213.
11. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry*. 2013;74:957–965.
12. Kirson NY, Weiden PJ, Yermakov S, et al. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. *J Clin Psychiatry*. 2013;74:568–575.
13. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168:603–609.
14. Mangalore R, Knapp M. Cost of schizophrenia in England. *J Ment Health Policy Econ*. 2007;10:23–41.
15. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382:951–962.
16. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2013;16:1205–1218.
17. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39:54–57.
18. Uggerby P, Østergaard SD, Røge R, Correll CU, Nielsen J. The validity of the schizophrenia diagnosis in the Danish Psychiatric Central Research Register is good. *Dan Med J*. 2013;60:A4578.
19. Uggerby P, Nielsen RE, Correll CU, Nielsen J. Characteristics and predictors of long-term institutionalization in patients with schizophrenia. *Schizophr Res*. 2011;131:120–126.

20. Mohamed S, Rosenheck R, Harpaz-Rotem I, Leslie D, Sernyak MJ. Duration of pharmacotherapy with long-acting injectable risperidone in the treatment of schizophrenia. *Psychiatr Q*. 2009;80:241–249.
21. Olfson M, Marcus SC, Ascher-Svanum H. Treatment of schizophrenia with long-acting fluphenazine, haloperidol, or risperidone. *Schizophr Bull*. 2007;33:1379–1387.
22. Lieberman JA, Stroup TS, McEvoy JP, et al.; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223.
23. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*. 2006;63:1079–1087.
24. Lasser RA, Bossie CA, Gharabawi GM, Turner M. Patients with schizophrenia previously stabilized on conventional depot antipsychotics experience significant clinical improvements following treatment with long-acting risperidone. *Eur Psychiatry*. 2004;19:219–225.
25. Marinis TD, Saleem PT, Glue P, et al. Switching to long-acting injectable risperidone is beneficial with regard to clinical outcomes, regardless of previous conventional medication in patients with schizophrenia. *Pharmacopsychiatry*. 2007;40:257–263.
26. Fleischhacker WW. Second-generation antipsychotic long-acting injections: systematic review. *Br J Psychiatry Suppl*. 2009;52:S29–S36.
27. Lambert M, De Marinis T, Pfeil J, Naber D, Schreiner A. Establishing remission and good clinical functioning in schizophrenia: predictors of best outcome with long-term risperidone long-acting injectable treatment. *Eur Psychiatry*. 2010;25:220–229.
28. Covell NH, McEvoy JP, Schooler NR, et al.; Schizophrenia Trials Network. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. *J Clin Psychiatry*. 2012;73:669–675.
29. McEvoy JP, Byerly M, Hamer RM, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA*. 2014;311:1978–1987.
30. Nielsen J, le Quach P, Emborg C, Foldager L, Correll CU. 10-year trends in the treatment and outcomes of patients with first-episode schizophrenia. *Acta Psychiatr Scand*. 2010;122:356–366.
31. Kumar A, Strech D. Zuclopenthixol dihydrochloride for schizophrenia. *Schizophr Bull*. 2009;35:855–856.
32. Pechlivanoglou P, Vehof J, van Agthoven M, de Jong-van den Berg LT, Postma MJ. Diffusion of a new drug: a comparative analysis of adoption, treatment complexity, and persistence of risperidone long-acting injectable therapy in the Netherlands. *Clin Ther*. 2010;32:108–118.
33. Li H, Rui Q, Ning X, Xu H, Gu N. A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:1002–1008.
34. Fleischhacker WW, Gopal S, Lane R, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. *Int J Neuropsychopharmacol* . 2012;15:107–118.